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Experimental Serum Disease: Large quantities of antigen injected intravenously cause characteristic tissue changes. If whole bacteria are injected, the recipient develops mesenchymal reactions especially in lungs, spleen, and liver. If serum is used, the recipient may acquire serum disease with special involvement of skin, lymph nodes, joints, heart, lungs, spleen, and kidneys. The present discussion is limited to the reactions caused by dissolved antigens.

The experimental lesions caused by large doses of serum or other dissolved antigens given intravenously closely resemble those of human serum disease, rheumatic fever (or rheumatoid arthritis), glomerular nephritis, and periarteritis nodosa.

It is noteworthy that the literature contains no attempt to distinguish between the various lesions from the pathogenetic point of view. Rich commented on the variety of organs involved saying that the differences in organs affected in different rabbits were possibly due to heredity. Hawn and Janeway who used pure albumin and globulin fractions in their experiments, found that albumin affected the arteries especially, whereas globulin damaged the glomeruli and the myocardium especially. When commenting on these results they expressed the view that the organ differences were possibly due to chemical differences in the antigens used.

The various tissue changes caused by serum have all been explained by allergy, or more precisely, by the anaphylactic type of hypersensitivity. It has been assumed that the antibodies elicited by the serum became fixed in or on the cells of the vascular connective tissue, and that the lesions were due to an Arthus phenomenon, that is to say to an antigen-antibody reaction in or on these cells. Such a reaction could be brought about either by a second injection of antigen after abundant antibody had been fixed after a first injection, or by a single injection if antigen was still in circulation when antibody was formed and laid down. The simultaneous occurrence of antigen and antibody after intravenous injection of serum has been demonstrated repeatedly.

It had been observed previously, however, that many of these lesions appear within 24 hours and reach considerable intensity within 3 days after a single injection of antigen. As they appear before significant quantities of antibody could have formed, they were interpreted as primary reactions of the organism to bacteria or their products or as representing the nonspecific reaction of the animals in the process of disposing of certain foreign materials injected into the blood stream. It is of interest that some of these reactions have recently been interpreted as morphologic expressions of antibody production.

The experiments reported upon in this paper and which were all performed in rabbits have shown that the intravenous injections of large doses of serum cause a great variety of reactions in the vascular connective tissue, notably of the right heart, the lungs, the kidneys, and the spleen. The frequency and intensity

of these reactions varied with the dose of serum injected. Twenty ml. of serum per kg. was more effective than 10 ml.; smaller doses were quite ineffective. The development of the lesions depended also on the age of the animals. Old rabbits with an average weight of 3.4 kg. reacted distinctly less, both serologically and morphologically, than young ones weighing from 2.0 to 2.4 kg. Some of the old rabbits also showed mild spontaneous mesenchymal reactions in heart and lungs, considered to be a result of previous infections.

The most pronounced lesions developed along the path of the injected antigen from the ear vein through the right heart into the lungs; beyond the lungs the spleen and kidneys were most markedly affected. In this respect, serum disease differs from the reactions to corpuscular antigens which appear chiefly in lungs, spleen, and liver. The two differ also in that allergic arteritis has not been observed following single or repeated doses of corpuscular antigen.

The authors consider that the differences in reaction to serum and corpuscular antigen are due to the differing particle sizes of the antigenic materials, for if whole bacteria or other corpuscular antigens are injected intravenously, they are taken up by the granulocytes and macrophages, which accumulate particularly in lungs, spleen, and liver. It appears that after they have been broken up by these cells, antigen is gradually released and induces antibody formation or is metabolized or excreted, especially by liver and kidneys. Antibody formation under these conditions takes place particularly in the spleen.

If dissolved antigens such as horse serum are used, some molecules reach the spleen where they induce antibody formation. Others on their way from the injected vein, infiltrate the right heart, the lungs, and other tissues, by reason of their much smaller molecular weight. Here they enter the lymph vessels and on their way through the regional lymph nodes reach the antibody-forming cells in these nodes. Still others go to the kidneys and liver to be excreted and metabolized. That this is the course of events, seems evident from recent work with radioactive antigen and from work with heparin, the fate of which is easily studied with the aid of toluidine blue. In the case of dissolved antigens, antibody formation seems to take place in the lymph nodes as well as in the spleen and most likely also in the heart, lungs, and other tissues.

It appears that many of the various lesions here reported are identical with those encountered in human serum disease by Clark and Kaplan who concluded that the changes did not correspond with those of early rheumatic fever, but they were uncertain of their character.

Subsequently, Rich and Gregory stated their belief that the myocardial and valvular lesions now in question were the same as those of rheumatic fever. It is true that in certain animals the authors have obtained lesions that closely resembled Aschoff bodies. Although some of these may well be an equivalent of rheumatic fever lesions, it should not be overlooked, that the common myocardial

changes in animals and man following the intravenous injection of large doses of serum are not usually seen in rheumatic fever, nor is allergic arteritis a usual feature of rheumatic fever. In fact, it may be worth questioning whether the experimental lesions do not correspond to those of rheumatoid arthritis in man rather than of rheumatic fever.

The authors consider that it is clear that the allergic arteritis of their experiments corresponded to human periarteritis nodosa, as generally contended, and that the two varieties of glomerular nephritis resembled the intra- and extracapillary types of glomerular nephritis in man.

Concerning the pathogenesis of the various lesions, it has been well known since the turn of the century that in man the intravenous injection of a large dose of serum may be followed, mostly within from 8 to 12 days by fever, urticaria, some proteinuria, enlargement of lymph nodes, and joint pains. In rabbits it may be followed, generally within from 5 to 6 days by fever, erythema, and edema of the ears, and transient proteinuria. It was observed by Derrick, Hitchcock, and Swift that in man urticaria and adenopathy preceded arthritis. It has also long been known that in animals from 10 to 13 days have to elapse before skin hypersensitivity can be demonstrated.

Concerning the serological aspects of these phenomena, it is known that precipitins become demonstrable in the circulating blood only when serum disease is in progress, that severe serum disease develops only in the presence of a good antibody titer, and that recovery from this disease is conditioned by the disappearance of antigen. It is also known that early in precipitin formation antigen and antibody may be present simultaneously in the blood without reacting with one another.

In the present series of experiments, fever, erythema and edema of the ears, and transient proteinuria were observed from 5 to 7 days after one injection of serum, antibodies were demonstrated after 5 days, and skin sensitivity after from 11 to 12 days. This falls in with previous findings already mentioned.

Fox and Jones and Hopps and Wissler have noted that there is no consistent correlation in frequency and intensity between ear reaction, skin sensitivity, precipitin titers, and morphologic changes in the rabbit, other than a gross correlation between precipitin titers, mesenchymal reactions, and allergic arteritis. However, the time of appearance of the various phenomena in the present experiments has made it evident that the common mesenchymal reactions in heart, lungs, and spleen commence before the appearance of serum disease, that is to say, when antibodies are not yet demonstrable, that serum disease develops at the time of maximum antibody formation which in rabbits occurs on the 5th and 6th days, and that subacute allergic arteritis occurs only after serum disease has passed and skin sensitivity has appeared, a happening which indicates that considerable quantities of antibody have been laid down in

the vascular connective tissue. Necrotizing myocardial lesions, and valvular ones were observed only after the animals had become sensitive. Similarly, severe proliferative glomerular nephritis was observed only at this later stage; degenerative changes and mild proliferation were already to be seen during the stage of serum disease. Necrotizing arteritis and extracapillary glomerular nephritis were seen only after a second injection of serum in sensitized animals.

It thus appears that allergic arteritis is a true Arthus pheonomenon, and that there are at least two Arthus phenomena, namely, a subacute and a recurrent one. Similarly extracapillary glomerular nephritis is to be interpreted as an acute Arthus phenomenon.

The authors state that they have no evidence that the mesenchymal reactions in myocardium, lungs, and spleen, which commenced before the onset of serum disease, were allergic. Since they occurred when the first antibodies were produced in the tissues, and the lesions contained abundant lymphoid cells, notably plasma cells, it seems likely that Bjørneboe and Gormsen were correct in their assertion that these proliferative reactions had to do with the production of antibodies rather than that they were the results of antigen-antibody union. The validity of this view has been further substantiated recently by Fagraeus.

Concerning the necrotizing lesions in the myocardium, and the more severe proliferative changes in the glomeruli, their time of appearance as well as their frequent association seems to indicate that they too were subacute Arthus phenomena, at least in part. (J. Exper.Med., 1 Jan. '49 - W.E. Ehrich et al.)

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Suppression of Shwartzman Phenomenon by Nitrogen Mustard, Benzol, and X-Ray Irradiation: When a filtrate of Eberthella typhosa is injected intradermally into a rabbit and 24 hours later injected intravenously, there develops a severe hemorrhagic necrotic reaction at the site of the intradermal injection within a period of from 2 to 6 hours. Shwartzman made his original observations on this reaction in 1927. It was soon found that many unrelated bacteria were capable of producing the reaction, including the Neisseria intracellularis, as well as nonbacterial substances, such as agar and starch. Although a certain small number of rabbits are naturally resistant to the reaction, a filtrate or endotoxin of a virulent meningococcus will consistently produce strong reactions in from 90 to 100 percent of rabbits tested.

Although the histological reaction is basically one of vascular injury, opinions differ concerning the nature of the Shwartzman phenomenon. There is agreement, however, that it is a nonspecific reaction which does not involve the known immunological mechanisms (agglutinins, precipitins, etc.). Because of the known depressive effect of Benzol, X-ray irradiation, and nitrogen mustards on the parenchymatous elements of the blood-forming organs and on the reticuloendothelial system, these agents were employed in an effort to throw

light on the nature of the Shwartzman reaction.

In this study male albino rabbits weighing from 2 to 3 kg. were used. The hair on the abdomen was removed with electric clippers. No depilatories were used and no shaving was done. Intradermal injections of 0.3 c.c. of undiluted meningococcus filtrate or endotoxin were made in 3 different areas, the epigastrium and the right and left lower quadrants. The primary reactions resulting from the intradermal injections usually consisted of erythema and varying degrees of edema which would fade gradually over a 48-hour period if not followed in from 24 to 48 hours by injection of the reacting factor intravenously.

From 20 to 26 hours after the intradermal injection, 2 c.c. of undiluted meningococcus endotoxin per rabbit, or 2 c.c. of the undiluted meningococcus filtrate per kilogram of body weight was injected into the ear vein. A small percentage of the rabbits died within the first few hours after this injection from the inherent toxicity of the undiluted filtrate or endotoxin. Dilution was avoided to insure as high a percentage of severe reactions as possible.

The effects of various agents and methods were studied to determine their suppressive action on the Shwartzman phenomenon. It was found that benadryl, urethane, crude penicillin extract, penicillin G, streptomycin, mapharsen, BAL, vitamin C, alpha tocopherol, thyroidectomy, and partial exsanguination were without suppressive effect. However, the reaction was completely suppressed by pretreatment of the rabbits with nitrogen mustard or benzol. It was also completely suppressed in some rabbits and partially in others by pretreatment with total body X-ray irradiation.

It is postulated that the mechanism of suppression by these agents is exerted through their specific but common suppressive action on the reticuloendothelial system, primarily the vascular endothelium. Because endothelial cells are rendered anergic, they are not able to react to the active principles in a way that otherwise would be self-destructive.

The Shwartzman phenomenon may then be interpreted as a local intracellular defensive but self-destructive reaction of the vascular endothelium to the bacterial active principles, and not, as a reaction resulting from the direct toxic effects of these bacterial products on the cells. Thus, when the ability of the cell to react is interfered with or suppressed in a specific way, as exerted by nitrogen mustard, benzol, or X-ray, the integrity of the cell is maintained and a destructive process avoided.

It is suggested that this study provides an experimental basis for a new therapeutic concept in the treatment of diseases involving tissue and vascular reactivity to known and unknown toxins. This concept would be directed toward suppressing the ability of the vascular endothelium to react adversely to whatever circulating toxin might be the inciting agent. A group of these diseases would include active rheumatic fever, acute, subacute, and chronic disseminated

Lupus erythematosus, periarteritis nodosa, generalized vascular diseases due to hypersensitive reactions to drugs, sera or vaccines, and probably dermatomyositis, rheumatoid arthritis, and acute and subacute glomerulonephritis. A recent case report by Osborne and associates of the successful response of a patient with chronic disseminated lupus erythematosus to nitrogen mustard would seem to provide confirmatory evidence in support of the therapeutic concept postulated above. (Proc.Soc.Exper.Biol. & Med., Nov. '48 - R.M. Becker)

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Intravenous Neostigmine in Diagnosis of Myasthenia Gravis: The purpose of this paper is to present a modification of the neostigmine diagnostic test, described by Schwab and Viets, which consists of the intramuscular injection of 1.5 mg. of neostigmine methylsulfate combined with 0.6 mg. of atropine sulfate, followed by an hour of observation at 10-minute intervals and scoring the patient on both the subjective and objective improvement. In the experience of the author and coworkers with this test, the initial response began in from 15 to 30 minutes and maximal improvement was unpredictable, often coming an hour or more after injection.

Based upon the studies that had been carried out by various workers, it seemed that the promise of a better diagnostic test using neostigmine intravenously offset what appeared to be a minimal risk. As neostigmine is apparently twice as toxic intravenously it was decided that only one third the intramuscular dose should be used. Accordingly, on 8 June 1942, 0.5 mg. (1 c.c. of 1/2000 solution) of neostigmine methylsulfate was given intravenously to an 18-year-old girl complaining of ptosis, diplopia, dysarthria, dysphagia and general incapacitating muscular weakness of four years' duration. Within 15 seconds she said distinctly, "I don't see double anymore." Within two minutes her ptosis and myasthenic facies had disappeared completely, and she demonstrated normal muscle power and swallowing ability. There were no untoward reactions to the drug.

In performing the intravenous test, a thorough history is taken with special emphasis on ptosis, diplopia, dysarthria, dysphagia and general muscular weakness variable with rest and fatigue, menstruation, pregnancy, acute infections and emotional upsets. On examination, a study should be made of the degree of ptosis, limitation of extraocular movements, ability to smile, whistle, distend the cheeks, chew gum, swallow liquids, count to 100, maintain grips, lift, walk, and step up on a chair or stool. Each of these performance tests should be repeated sufficiently to detect abnormal fatigability. The results should be carefully recorded.

If the history and physical findings are sufficiently characteristic of myasthenia gravis, 1 c.c. of a 1/2000 solution (0.5 mg.) is injected intravenously within a timed one minute period. Improvement in a true case of myasthenia gravis often begins before the needle can be withdrawn and is usually maximal

in at most five minutes. Therefore, the performance tests should be repeated after 5 minutes have elapsed and the degree of objective improvement recorded. Subjective improvement is not considered, thus lessening the possibility that a psychic response to an injection might result in a false positive diagnosis. Occasionally, in very mild true myasthenia gravis the response to an intravenous dose of 0.5 mg. of neostigmine is doubtful or minimal. In such an instance the test should be repeated on the following day with one mg. provided there were no untoward reactions to the 0.5 mg. dose.

Atropine sulfate, usually 0.6 mg., should always be kept at hand and should be injected subcutaneously whenever side-effects become manifest, but is never to be injected with the neostigmine. Viets has stated that marked side-effects from neostigmine almost disprove a diagnosis of myasthenia gravis, and the experience of the author and coworkers has been similar. However, these side-effects, although uncomfortable, are apparently not dangerous and the author does not, contrary to what Viets advises, use atropine simultaneously with neostigmine to offset them. The author and coworkers feel that these reactions, however, uncomfortable, are highly valuable diagnostically.

In the past five years the author and coworkers have given neostigmine intravenously on several hundred occasions, not only as a diagnostic test for myasthenia gravis but also to arthritics and in neuromuscular cases. The only side-effects worthy of note were encountered in non-myasthenic individuals and in those with extremely mild myasthenia gravis. These consisted of mild abdominal cramping, muscle fibrillations, flushing and sweating, dizziness, mild nausea and diarrhea. The heart rate was slowed but never more than 10 beats per minute and the drop in blood pressure was negligible. These reactions were stopped, without exception, within from 10 to 15 minutes by the subcutaneous injection of 0.6 mg. of atropine sulfate.

The author states that he and his associates have seen several patients with extremely mild involvement or in partial or complete remission, whose past history justified further study. In some of these even 1 mg. of neostigmine intravenously gave an indefinite response. In such cases the Curare test, the Jolly test, muscle biopsy and barium swallow under fluoroscopy have proved highly valuable. Also of some merit is a therapeutic test consisting of neostigmine bromide orally for one week.

Another example of the rapid effect of intravenous neostigmine is a 5-year-old boy who experienced a sudden onset of ptosis, dysarthria, dysphagia, and general muscular weakness on 7 November 1946. The referring diagnosis was tuberculous meningitis. On 20 November 1946, 0.25 mg. of neostigmine methylsulfate was injected intravenously and the patient showed complete recovery of all muscle function within three minutes. This rapid complete response was demonstrable not only in the facies and the extraocular muscles but also in masticatory, pharyngeal, laryngeal, and skeletal musculature.

Neostigmine intravenously has given better results in the performance of the fluoroscopic barium-swallow test for dysphagia than has intramuscular neostigmine. When barium is retained in the upper esophagus, 0.5 mg. of neostigmine is injected intravenously. If the dysphagia is due to myashenia gravis, a return to normal swallowing can be visualized in a few minutes instead of the 20 minutes or more required with intramuscular administration.

Intravenous neostigmine has been used by the author and associates in the diagnosis of 24 cases of myasthenia gravis in their series in the past five years. Of these, 21 or 87.5 percent, reacted sufficiently for a positive diagnosis. Only three patients failed to react. One gave a history of previous typical severe myasthenia gravis with respiratory failure requiring a respirator. She was seen in complete remission and failed to react to intravenous neostigmine. The Jolly and Curare tests were also negative but the finding on muscle biopsy was considered typical of myasthenia gravis. The second non-reactor had extremely mild symptoms. The Jolly and Curare tests were positive, however, and he has since responded well to oral neostigmine. The third non-reactor gave a typical history of previous severe myasthenia gravis but was seen in complete remission during his hospitalization for duodenal ulcer. His diagnosis was made on the basis of a typical history and positive Jolly and Curare tests. Objective improvement in all of the 21 reactors following 0.5 mg. of neostigmine intravenously was so rapid and clear-cut that no other diagnostic methods were necessary except otherwise to confirm a positive diagnosis.

The experience with intravenous neostigmine in the diagnosis of myasthenia gravis leads to the belief that it has the following advantages over the intramuscular diagnostic test: (1) It gives a more rapid complete response which lessens the possibility of a false negative diagnosis in a mild case; (2) Only objective responses need be considered which diminishes the risk of false positive diagnoses; (3) The quick, clear-cut response should facilitate office diagnosis by a busy practitioner and aid in demonstration of cases for teaching purposes. (Ann.Int.Med.,Dec. '48 - J.E. Tether)

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Dextran as a Plasma Substitute: In 1943 Grönwall and Ingelman, in Sweden, suggested the use of dextran as a substitute for plasma. This colloid is free from the drawbacks of other colloids previously prepared as substitutes for plasma.

The dextran now in use is a 6-percent solution of the polydispersoid glycose-polymer dextran, in which most of the molecules have been hydrolytically given a molecular weight conforming to that of albumin, with 0.9 percent of sodium chloride added to it. Its viscosity lies between that of blood and that of plasma,

and its specific gravity somewhat exceeds that of human plasma. Dextran is virus-free, does not lead to the formation of antigens, and contains almost no nitrogen. Its thread-like molecules are electrically neutral and chemically indifferent.

Dextran has been given to 5000 patients, 20,000 units having been infused. In a few cases up to 4 liters has been given in a single infusion. The largest amount given to any one patient has been 10 liters. Dextran is nontoxic and does not injure the tissues either locally or systemically. The results obtained with it have been very good both in the treatment and in the prevention of shock. At the Serafimer Hospital, Stockholm, Sweden, dextran is used as a routine in the prevention of shock during major operations. Rosenqvist has reported dextran to be as good as plasma in shock from burns. In Sweden today the hospital transfusion services rely to a large extent on dextran for emergency cases. Its use has not been found to affect fertility, fetal development, or growth.

After an intravenous injection of from one to 2 liters of dextran the plasma-dextran level rises to from one to 2.5 Gm. per 100 ml. Next, after an initial fall due principally to elimination of a low-molecular fraction through the kidneys, the plasma-dextran level falls at an even rate.

During the initial renal excretions of low-molecular dextran the urine-dextran level may rise to 7 Gm. per 100 ml. without any sign of renal injury. During this time about a quarter of the dextran given is excreted, provided an ordinary amount has been infused. After that no dextran can be detected in the urine by polarimetry, even though the plasma-dextran level remains relatively high. The mean molecular weight in the dextran excreted in the urine has been calculated at 25,000. Dextran of a higher molecular weight is presumably metabolized.

After the initial fall the plasma-dextran level falls at an even rate, which is more rapid in small animals than in large ones; the rate increases with the simultaneous administration of thyroid hormone, and is also related to the amount of dextran given.

The elimination of dextran not excreted in the urine takes place at a rate that differs slightly in different species of animal, as calculated per Kg. of body weight per day, irrespective of the amount given. In animals to which dextran has been given in repeated infusions, so that the total amount of dried substance corresponds to a third of the body weight, no dextran has been discovered in the brain, lungs, heart muscle, liver, spleen, kidney, or bone marrow, either by morphological changes or in watery extracts from the organs after it has disappeared from the plasma.

The infusion of a noncolloid solution lowers the colloid osmotic pressure more than it reduces the plasma-colloid level. The lowering of the colloid-osmotic pressure often deleteriously affects cellular metabolism, because the conditions requiring an infusion are often those associated with capillary injuries, and

consequently with disturbed colloid-osmotic pressure. This reduction in pressure can be counteracted and neutralized by giving parenteral dextran. This has produced notable results, especially in paralytic ileus, when the re-absorption of edema fluid in the intestinal wall, following the increased colloid-osmotic pressure, has manifested itself by restored intestinal motility. In hypo-proteinemia with edema the urinary excretion is increased.

The normal colloid osmotic pressure, however, can be raised only slightly. If additional amounts of dextran are given, only temporary increases in pressure are obtained, and the plasma-dextran level can be raised above 3.5 Gm. per 100 ml. for only a very short time. The excess of dextran rapidly disappears from the circulation. The plasma-dextran level after such amounts decreases slowly, the time taken for it to disappear corresponding to the quantity given. But the rate of elimination expressed in Gm. per kg. of body weight per day, is the same, irrespective of the initial amount infused.

Flooding of the extravascular space with dextran has not given rise to definitely unfavorable effects in the test animals, but it produces edema. Such large amounts of dextran are not used clinically.

A raised plasma-dextran level is always associated with lowered plasma-protein level. When later the plasma-dextran level falls, the plasma-protein level rises again.

No unfavorable effect from the simultaneous fall in the plasma-protein level has been noted clinically, even though the plasma-protein level has fallen to 2 Gm. per 100 ml. No sign of disturbed coagulation or reduction in the resistance to infection, in the formation of antibodies after the injection of tetanus and diphtheria anatoxin (Heinertz and Thorsen unpublished), or in the tensile strength of wounds after operation has yet been noted either clinically or experimentally after the administration of dextran in therapeutic doses.

The factors, principally dilution and colloid-osmotic pressure, acting as mentioned above as well as on the reciprocal concentration of the different fractions of plasma-proteins, have been investigated by Thorsen and Malmros (unpublished). (Lancet, 22 Jan. '49 - G. Thorsén)

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Dextran as a Plasma Substitute: Swedish workers, after very extensive clinical trials, have reported favorably on dextran solutions prepared in Sweden. Dextran has certain theoretical advantages over other nonprotein colloids in that (1) it is free from acidic radicals, and therefore not likely to form storage complexes, and (2) it can be hydrolyzed into glucose by acids and by certain living organisms which suggests that the human body may also be able to metabolize it slowly.

During the 1939 to 1945 war, human plasma and serum were prepared in large amounts, and as they are now widely available it might seem superfluous to pursue the search for a really satisfactory substitute for plasma. However, plasma and serum carry a definite though small risk of infecting the recipient with hepatitis or some other transmissible disease. Moreover there are climatic and geographical circumstances in which a stable plasma substitute which could be manufactured in unlimited amounts might be very valuable. Even where blood and plasma are readily obtainable, and even if it should prove possible to free plasma from all infective agents, it might still be an advantage to have reserves of a plasma substitute for use in some civil or military emergency. The main function of the substitute would clearly be to restore circulating blood volume until the patients' own plasma-protein returned to the circulation. Such a substance would suffer from the theoretical disadvantages of being unable to fulfil the nutritive, buffering, or immunological functions of plasma-protein; but, since usually it would only be taking the place of plasma-protein for a matter of hours, this could not be considered an important objection. It is also clear that a plasma substitute can never be more than second best when the patient has lost whole blood rather than plasma, and that infusion of plasma substitute in such cases would have to be followed by transfusion of whole blood to secure the best clinical response.

The theoretical requirements of a plasma substitute are as follows:

(1) Its colloid solutes should be retained in the circulation until their place can be taken by the natural proteins. This implies that (a) the colloids should not pass readily into the tissue fluids nor be rapidly excreted by the kidney (a molecular size of at least 70,000 is therefore usually desirable); and (b) the colloid substance should not be rapidly metabolized or otherwise removed by the tissues.

(2) The solution used for infusion should have an osmotic pressure and viscosity similar to those of plasma.

(3) The composition from batch to batch should be constant, within narrow and definable limits.

(4) The material should be stable during storage and preferably not require special conditions of temperature.

(5) It must not be toxic, either locally or generally.

(6) It must not induce fever.

(7) It must not induce sensitization.

(8) It must not be stored for long periods in the tissues.

(9) It must not act as a diuretic. Apart from the absence of specific diuretic properties, this implies that it should not contain large amounts of solutes of low molecular weight.

All these requirements could be met by a solution of nontoxic nonprotein material of suitable molecular weight which was slowly metabolized by the tissues. For maximum osmotic effect with the minimum of material, while still satisfying criterion (1)(a), the range of molecular size should approximate that of

plasma-albumin. The present study shows that dextran preparations can fulfil most of these requirements.

In 1946 the Swedish firm, Pharmacia A.B., generously supplied some of their dextran, and it was possible to give this to a few patients and confirm that it was a bland fluid which produced favorable clinical results. Shortly afterwards dextran manufactured experimentally in Britain became available, and it was possible to begin a more extensive trial.

Dextrans are produced by the growth in culture of various micro-organisms, particularly by the nonpathogenic coccus, Leuconostoc mesenteroides, in a substrate of sucrose and phosphate. The micro-organism produces an enzyme or enzymes which synthesize dextran from sucrose. After removal of protein and inorganic salts from the culture fluid, dextran is precipitated in the form of a syrupy gum by organic solvents such as acetone; so obtained, it is a polysaccharide composed entirely of glucose units. Each unit is joined by an alpha-glucosidic linkage to the primary alcoholic hydroxyl group of its neighbor. The long chains thus constituted may have occasional branch linkages to adjacent chains through other secondary hydroxyl groups. As with many other polysaccharides, the details and degree of this branching are uncertain.

Swedish workers tested this material for infusion but soon found that the molecules of crude dextran were too large for this purpose. More encouraging results were obtained with preparations whose average molecular size had been reduced by partial hydrolysis with acid. The authors use the term "undegraded dextran" for the polysaccharide synthesized from sucrose, and "dextran" for the degraded product produced by acid hydrolysis.

Based upon the results of the studies carried out, the degree to which dextran fulfils the theoretical requirements laid down above can now be discussed.

Dextran is well retained in the circulation, and the observations of the authors show that it can maintain the osmotic pressure until its place is taken by the plasma-proteins. The slow rate of disappearance of dextran from the plasma shows that it does not pass rapidly into the tissues. However, a significan proportion, amounting to some 25 percent in most of the batches tested, does escape into the urine soon after infusion. In one case it was possible to demonstrate that the dextran escaping into the urine was of lower molecular weight than the average of the dextran infused. It is clear that the greater the proportion of dextran of molecular size which will pass the glomerular filter, the less the value of dextran as a substitute for plasma becomes. On the other hand, Grönwall and Ingelman have found that, if the molecular weight of dextran is insufficiently reduced during the stage of acid hydrolysis, the resulting product causes renal damage. Thus it is desirable to prepare dextran with a defined range of molecular size. Further, a uniform preparation is required if reproducible clinical effects are to be obtained. At present details of a specification are being worked out in collaboration with the manufacturers. Limits for the range of molecular size

and for the mean will be defined by practical physicochemical tests; and there will probably be further biological criteria depending on injections into animals. Such a specification should ensure a standard of consistent physiological efficiency not hitherto attained in a fluid used for artifical resuscitation. In developing this specification it will probably be best to lower slightly the total content of sodium chloride and dextran; in the experiments on animals it was noted that restoration of blood pressure was more rapid after dextran infusion than after blood transfusion; and in the clinical trials a secondary rise in blood pressure after the infusion of dextran was sometimes observed, suggesting that fluid was being drawn into the circulation.

Though dextran appears to possess the positive qualities required of a plasma substitute, one important doubt remains on the negative side, namely, the ultimate fate of dextran in the body. No evidence has been obtained to support or disprove the statements of Grönwall and Ingelman that dextran is metabolized, probably as glucose. The experiments in which dextran was incubated with extracts and suspensions of liver and pancreas indicate that its degradation in the body is unlikely to be rapid. In rabbits injected with dextran, the dextran remaining in the body, after the excretion by the kidney of the material of small molecular weight passes into the tissues, particularly into the reticulo-endothelial system. In the course of eight weeks, under the conditions of these experiments, the concentration falls gradually, but even at the end of this period dextran can still be detected by the serological method, especially in the lymph glands and spleen, when it can no longer be detected in the plasma. This evidence suggests that dextran gradually disappears from the body, but a definite statement cannot be made until further experiments have been made to show whether its disappearance is complete.

Several possibilities regarding the fate of dextran in the body suggest themselves:

(1) The retained polysaccharide may be broken down slowly and metabolized as glucose. Swanson has shown that undegraded dextran is resistant to alpha and beta amylase, muscle, and potato phosphorylase. The 1-6 linkage, which predominates in dextran molecules, appears to resist enzymic hydrolysis, or perhaps the configuration of the molecule is such that enzymic action is inhibited; but this does not necessarily mean that degradation in the body will not eventually take place.

(2) The retained polysaccharide may be slowly broken down to a molecular weight less than 70,000 and excreted by the kidneys.

(3) Part of the retained polysaccharide may be excreted after suitable degradation, the remainder being burnt as glucose.

The fate of the retained material is of great importance, for the ideal substitute for plasma should be completely metabolized or excreted. Until its fate in the body is known, dextran cannot unreservedly be recommended as a substance for intravenous infusion. With this proviso, a dextran solution with the characteristics described appears to be free from the disadvantages of other non-protein substitutes for plasma.

Dextran has proved efficacious as a plasma substitute in cases of burns, and has produced a sustained increase in the venous return in patients with surgical shock or hemorrhage. (Lancet, 22 Jan. '49 - Bull, Ricketts and Squire of the MRC Burns Unit, Birmingham Accident Hospital, Maycock and Spooner of the Lister Institute, and Mollison and Paterson of the MRC Blood Transfusion Research Unit and Department of Medicine and Surgery, Postgraduate Medical School of London)

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Massive Picrotoxin Therapy in Acute Barbiturate Poisoning: The purpose of this presentation is to describe the authors' experience using massive doses of picrotoxin in the treatment of 30 patients with acute barbiturate intoxication who have been seen since 1 January 1946.

It is usually difficult to determine the amount of barbiturate consumed and the time elapsed before hospitalization, so that the severity of the poisoning must be judged from the initial observations and the subsequent course. Intoxication was considered to be severe (1) when more than from one to 2 Gm. of a barbiturate was ingested, (2) when unconsciousness prior to hospitalization was prolonged, (3) when coma was associated with absence of reflexes, and (4) when respiratory depression was present.

On the patient's admission to the hospital a rapid appraisal was made of his condition and depth of unconsciousness. This appraisal included principally a neurologic examination, determination of blood pressure and examination for signs of inadequate respiratory exchange, such as pharyngeal and tracheal obstruction or cyanosis. The immediate therapy was based on findings from these examinations. General supportive measures were instituted at once. For respiratory embarrassment and peripheral circulatory collapse the patients were provided with an adequate airway (nasal or endotracheal), oxygen inhalations, and intravenous administration of fluids. For several patients with respiratory depression the use of artificial respiration was necessary in conjunction with the administration of respiratory stimulants and analeptic drugs.

Gastric lavage was performed for most of these patients, in spite of the fact that they were unconscious many hours prior to admission. While the gastric tube was in place a saline cathartic was frequently administered. Samples of the gastric juice and urine were tested for barbiturates. If there was any doubt of the diagnosis, a spinal puncture was performed in an attempt to rule out any other intracranial pathologic condition, e. g., hemorrhage.

Frequent aspiration of mucus from the throat was continued as long as the patient was unconscious. The Trendelenburg position was often useful in preventing aspiration of secretions. Because of the high incidence of pulmonary complications, penicillin therapy was instituted for these patients from the time

of their admission, even though they were afebrile and presented no signs of such a complication. Frequent turning of the patient in bed was also helpful in this regard.

Analeptic drugs are the vital part of therapy in severe barbiturate intoxications. Picrotoxin was used almost exclusively for the patients in this series, although at times it was supplemented with metrazol, desoxyephedrine hydrochloride, and amphetamine. While a patient is comatose, there is no toxic dose of picrotoxin until a preconvulsive state is reached. The individual dose of picrotoxin for these patients varied. Amounts ranging from 9 to 45 mg. per dose given intravenously at 15-minute intervals were necessary to obtain the desired degree of stimulation. Once intravenous administration of fluids was started, all medicaments were injected into the rubber tubing to save veins for future use and to avoid excessive trauma. As the patients improved, the amount of drug was progressively decreased, according to the response of irritability obtained from the picrotoxin. After muscular twitching was once obtained, the therapy revolved about maintenance of constant irritability and twitching just below the convulsive threshold. In spite of all precautionary measures, however, many of the patients had short convulsions; there were apparently no untoward effects from these episodes.

In several of the cases reported upon in this paper, amphetamine was used with the picrotoxin. The chief rationale for the use of amphetamine was that it stimulated the depressed cerebral cortex thereby supplementing picrotoxin, which acts mainly on the lower brain centers.

A third analeptic agent, metrazol, has also been employed as a stimulant of the central nervous system. The rapid response to this drug may be utilized as an aid in the determination of the depth of coma. At periodic intervals while patients were receiving active picrotoxin therapy, they were given one c.c. (100 mg.) of metrazol intravenously and the response observed. If no reaction was elicited, the dose was progressively increased to 3 c.c. and the response was graded accordingly; thus, a crude estimate of the degree of depression of the central nervous system could be made.

The presence of peripheral vascular collapse was a common complication in the severer intoxications. The therapeutic agents employed, besides analeptic stimulants, included plasma, isotonic solution of sodium chloride and whole blood, the amount depending on the patient's condition. A recent addition to these chemotherapeutic agents was desoxyephedrine hydrochloride, which was used both for its stimulating action on the central nervous system and for its effect of raising blood pressure.

Some of the problems encountered in these cases is revealed in the following:

Case 11. This patient, a 30-year-old white woman, was hospitalized about five hours after having taken approximately 150 grains (9.72 Gm.) of phenobarbital. The initial response to 15 mg. of picrotoxin given intravenously was good, that is, twitching resulted. Within from eight to ten hours, however, extreme deterioration occurred. Whereas corneal and gag reflexes were present on her admission, these could no longer be elicited, and respiratory depression had become pronounced. A test dose of 1 c.c. metrazol administered intravenously along with the picrotoxin on her admission had evoked a brief convulsion; but now the patient was no longer stimulated by 3 c.c. of metrazol, which signified roughly the increasing depth of coma. Because the patient no longer responded to the orthodox therapy recommended, we felt that more radical doses must be administered. The usual 15 mg. dose was progressively increased to 45 mg. (15 c.c.) every fifteen minutes. At this level, a preconvulsive state was obtained. Clinically, the patient showed early signs of improvement with the elevated dose; the blood pressure rose, and the respiratory excnange was improved. In the course of several hours this dose was reduced slowly to lower levels, with constant maintenance of an irritable state. The patient received more than 15 mg. of picrotoxin every fifteen minutes for more than one hundred and four hours. At the end of the fifth day of unconsciousness, the patient opened her eyes and responded to simple instructions. An attempt was made to stop all therapy, but within one hour the patient slipped back into coma, and vigorous therapy was again resumed. By the end of the next twenty-four hours the patient was talking and sipping fluids, but constant stimulation was required to maintain this state for another twelve hours. The fact that barbiturates were present in the urine on the eighth day after her return to consciousness explained the necessity for constant stimulation to prevent relapse. This case, like many others, was complicated by extensive bronchopneumonia. Penicillin and streptomycin were given from the beginning of therapy, in spite of which the patient's illness ran a stormy, febrile course. Aerosol penicillin was instituted once the patient was conscious to help stem the severe bronchopneumonia. During the period of unconsciousness, an acute gastric dilatation occurred, requiring Wangensteen suction for several days. The patient received 14,196 mg. of picrotoxin, and 1,950 mg. of amphetamine were given concomitantly in doses of 10 to 30 mg. intravenously. It is believed that this total dose of picrotoxin is the highest recorded in current literature. At the end of two weeks the patient was no longer considered a medical problem and was transferred to the department of psychiatry.

It should be emphasized that after the patient begins to respond to smaller and smaller doses of picrotoxin with preconvulsive twitchings, indicating an awakening of the lower brain centers, therapeutic stimulation of the cortex by amphetamine is indicated, because picrotoxin is not primarily a cortical stimulant. If all medication is stopped as soon as the patient begins to awaken, he will go back into coma, especially when barbital or phenobarbital has been ingested, for these drugs are excreted slowly.

Maintenance of fluid balance, constant vigilance in keeping the air passages clear and, above all, immediate administration of antibiotic substances to help prevent pulmonary infection are necessary if the analeptic agents are to have a chance to reverse the intoxication. If these measures are not instituted, the patient may die before sufficient time has elapsed to allow neutralization of the intoxicants.

Following medical therapy, these patients should be given psychiatric care. (Arch. Int. Med., May '48 - E. A. Newman and M. Feldman)

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The Use of Quinidine Sulfate in the Treatment of Hiccup - A Preliminary Report: This report is based on experience by the authors working in the Division of Cardiology, Philadelphia General Hospital and the Edward B. Robinette

Foundation of the University of Pennsylvania in the use of quinidine sulfate in the treatment in 9 cases of persistent hiccup. In 6 of these cases, the drug proved effective, in 2 the hiccup was improved but did not stop altogether, and in one this treatment was apparently of no help.

Hiccup has been described as an intermittent clonic contraction of the diaphragm often associated with clonic contraction of the accessory muscles of respiration, or as a sudden clonic spasm of the diaphragm accompanied by a spasmodic closure of the glottis. It is due to a great variety of causes which irritate either the afferent pathway to the centers in the upper cervical part of the spinal cord, the centers themselves or their efferent pathways to the muscles. Reflexes through the vagus may play a part in its production. Kremer was of the opinion that the clonic contraction of the diaphragm is set off by an irritation of the respiratory center. This can be initiated by: (a) disturbance in the central nervous system; (b) a chemical irritation resulting from anoxemia, uremia, and toxic products; and (c) by stimulation of the sensory fibers of the phrenic and sympathetic nerves and also by reflexes through the peripheral nerves.

A multitude of conditions such as a diseased state in the abdomen, chest or brain, and systemic infections as well as psychologic factors may incite the attacks. Among the frequent conditions which precipitate these seizures are disorders of the esophagus and stomach, such as gastritis and gastric dilatation, intestinal obstruction, ileus, strangulated hernia, acute appendicitis, acute pancreatitis, peritonitis, renal disease with azotemia, liver disease, tumors and inflammatory disease of the mediastinum, disease of the heart and pericardium, brain tumor, meningo-encephalitis, epidemic encephalitis, cerebrovascular accident, typhoid fever, and other severe infections.

Among the procedures commonly mentioned in treatment are: pressure upon the phrenic nerve between the heads of the sternocleidomastoid muscle, drinking cold water, holding the breath or the induction of sudden fright. Gastric lavage will often give relief when irritation of the gastric mucous membrane is present. Apomorphine, gr. 1/8 hypodermically, or hyoscine hydrobromide, gr. 1/200, may be given and repeated after 3 hours. Morphine by itself rarely succeeds in stopping an attack. Benzyl benzoate (1/2 dram of a 20-percent solution) sometimes stops the attacks. Inhalations of amyl nitrite and chloroform have been used. Application of an ice bag to the neck, ethyl chloride sprayed on the epigastrium, repeated traction of the tongue, pressure on the eyeballs, mechanical dilatation of the esophagus, and pressure upon the ribs near the origin of the diaphragm, have all been tried. Inhalation of from 5- to 10-percent carbon dioxide in oxygen may be pursued until the patient has had an absence of hiccup for a one-minute period. If hiccup recurs, as it often does, inhalation of carbon dioxide should be started again. In intractable cases, it has been suggested that the patient be examined fluoroscopically to determine the side of the diaphragm involved and then the phrenic nerve on the affected side be exposed, anesthetized, and crushed or avulsed. Occasionally, bilateral

phrenicotomy has been performed. Because this procedure results in decreased pulmonary ventilation on the affected side and may further embarrass an already impaired cardiovascular system, this method should be carefully considered before it is used.

The usual well-known methods of treatment of hiccup were tried first in most of these 9 patients, with little or no success. The authors' experiences in this series of cases suggest that quinidine has an apparently beneficial effect in controlling attacks of hiccup. In these 9 patients the drug was given by mouth, intramuscularly, and in one patient, intravenously. Although it is felt that administration by mouth is effectual, its action is apparently more dependable when given by the parenteral route. By the intramuscular route the absorption is certain, uniform, and relatively safe. It is felt that a more effective response will be obtained by the use of large doses given over a relatively short period of time rather than small doses given over a prolonged period. That this drug may not work equally well in all cases will depend upon the underlying cause of the increased irritability and its degree. The authors are as yet not certain concerning the dose of the drug and frequency of administration which may be necessary to stop a paroxysm. At present it is suggested that an initial dose of 10 grains, preferably given by the intramuscular route, be repeated hourly for from 3 to 4 doses. If the paroxysm stops, the patient may be put on a maintenance dose of 5 grains orally every 2 to 3 hours. If the paroxysm recurs, the initial high doses should be repeated.

The use of quinidine is not recommended in all patients. It is suggested for use in those cases of persistent hiccup in which the usual procedures are ineffective and in which the continuance of the paroxysms results in exhaustion of the patient.

It has been shown that quinidine lengthens the refractory period of skeletal muscle; it decreases the ability of the muscle to respond to and hold a tetanus. The excitability of the motor-end plate is lowered, so that the response to nerve stimulation is reduced. This is best seen in a partially curarized muscle. When quinine is injected under these conditions, the curarization becomes complete. This action is also in part responsible for the abolition by quinine of the quick response of the muscle to injected acetylcholine. That quinine may have a direct effect on nerve tissue is suggested by Stravaky who found that quinine acts directly as a paralyzing drug on the secretory fibers of the auriculo-temporal nerves.

The normal potentiation of the twitches caused by physostigmine due to repetitive response to a single nerve volley is prevented by the previous administration of quinine or is counteracted promptly when the drug is injected during a period of potentiation. Weiss found that the fibrillary twitchings produced in the cat by prostigmine were abolished by the intravenous injection of quinine. The repetitive response to a single stimulus which occurs after veratrine is also removed by quinine. This occurs in both the normal muscle and

muscle of which the motor nerve has previously been cut and allowed to degenerate. Harvey has shown that the curareform action of quinine is greatly increased by the introduction of the quaternary ammonium ion in the quinoline ring as observed by the action of quinine methochloride. The main features of the action of quinine methochloride on the mammalian nerve muscle preparation resembles curarine, blocking neuromuscular transmission and leaving the response of the muscle to direct stimulation unimpaired. Like curarine, it causes a depression of the response of the motor-end plate and the ganglion cell to nerve impulses and to acetylcholine, but does not interfere with the normal liberation of acetylcholine from the preganglionic nerve endings. This drug has been used successfully in the prevention of fractures in the course of convulsive therapy with metrazol. Wolf showed the value of quinine in the treatment of myotonia congenita. The chief clinical manifestation in this condition is a contraction in skeletal muscle after the end of a voluntary stimulation. This state is symptomatically relieved by quinine but is made worse by prostigmine. Quinine increases the muscular weakness of patients with myasthenia gravis, thus manifesting an opposite effect to that of prostigmine in these 2 conditions. The cinchona drugs have also been of value in the treatment of night cramps of the lower extremities (News Letter of 9 April 1948, Vol. 11, No. 8). This condition appears to be due to a lasting tetanic contraction of a muscle group due to reflex bombardment of the myoneural junction by a stream of impulses from some neighboring source of irritation. The effectiveness of quinine in these cases is due in part to its action directly on muscle tissue, but more important is its effect in interrupting the reflex arc by blocking myoneural pulse transmission.

The authors believe that if attacks of hiccup are the result of spasmodic contractions of the diaphragm and other muscles of respiration, the impulses for which are transmitted through nerve tissue, quinidine could stop a paroxysm of hiccup in 2 ways: (1) by a direct effect of the drug on the diaphragm as well as on the other muscles of respiration; and (2) by blocking the nerve impulses at the myoneural junction. There is some suggestive evidence that this drug may have a direct effect on nerve tissue which may block impulses through the vagus and other nerves.

Since this paper was submitted for publication, the authors have observed in further studies that, in those patients in whom hiccup follwed abdominal operations and subsequent fluid loss by vomiting or other means, electrolyte imbalance, notably hypocalcemia and hypopotassemia, was apparently a factor which tended to induce or help maintain the attack of hiccup. In addition to the administration of quinidine, the correction of this electrolyte imbalance was an important factor in stopping the hiccup attacks. (Am. J. M. Sc., Dec. '48 - S. Bellet and C. S. Madler)

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Q Fever in Laundry Workers, Presumably Transmitted from Contaminated Clothing: Q fever is caused by Rickettsia burneti. It is known to occur in Australia, the United States, Panama, and in countries bordering the Mediterranean. The causative agent has been found in ticks of various species, in cattle, and cow's milk. The feces of infected ticks are infectious and may remain so for months. The dried urine and blood of experimentally infected guinea pigs have been demonstrated to retain infectivity for several weeks. Human infections have occurred chiefly in those associated with the packing and dairy industries, and in laboratory workers. Presumptive evidence has accumulated indicating that cases in man may be due to the inhalation of dried infectious material. For instance, in the laboratories of the National Institutes of Health, Bethesda, Maryland, and of the Rocky Mountain Laboratory, Hamilton, Montana, cases are known to have occurred in personnel not directly associated with units in which work with Q fever was being done and having no known direct contact with such units. To date, no reports have appeared of human infections acquired by contact with contaminated clothing and linens.

Recently, 3 cases of clinical Q fever and 3 cases of apparently subclinical Q fever have occurred in employees of a laundry in Hamilton, Montana, handling material from the Rocky Mountain Laboratory under circumstances suggesting that infection may have been transmitted to them by contaminated clothing and linens. There was no history of recent tick bite, exposure to contaminated air in experimental laboratories, contact with slaughterhouses or cattle pens among these individuals to account for infection arising outside their place of employment.

Material to be laundered, consisting of soiled coveralls, towels, and the like, was delivered to the laboratory stock room by the various laboratory units in individual cloth bags on the morning of the days collection was to be made. Upon collection and delivery to the laundry by one of the laundry workers, the material was sorted and marked on a table in the rear of a large room on the ground floor. Nine persons, including the manager, worked on this floor. Four persons were employed in a finishing room on the second floor. Of the 9 first-floor employees, 6, including the manager, handled soiled laundry at one time or another in the ordinary course of duty. Among these 6, there were 3 cases of Q fever; in the other 3, the sera of two had good titers of Q fever complement-fixing antibody and the third had a low titer when tested on 19 April 1948, although none of these latter 3 had had any known recent illness. The 3 who did not handle soiled laundry had no complement-fixing Q fever serum antibody.

Blood specimens were obtained 2 June 1948, from the 4 employees who worked on the second floor of the laundry. The sera of all 4 were negative for Q fever antibody by the complement-fixation test.

It is of interest that only those employees of the laundry who actually handled soiled laundry developed Q fever infection. Whether the infections were derived

from dust from the contaminated materials was not established. However, other persons working in the immediate area where the materials were processed were not infected.

The onsets in the 3 cases occurred on 13, 21, and 27 February. The intervals between these dates are within the limits of variation of the established incubation period of Q fever which is from 14 to 26 days. Thus, it seems unlikely that the second and third cases arose from contact involving the first patient.

No claim is made that a new mode of transmission of Q fever is established by the evidence presented. It is of public health significance that infection apparently can be transmitted indirectly by contact with contaminated materials such as clothing and linens. No other probable source of infection was established in the cases described.

All soiled laundry from the Rocky Mountain Laboratory is now routinely sterilized with steam under pressure before delivery to the laundry.

Treatment with penicillin, streptomycin, and sulfadiazine had no apparent effect upon the clinical course of the disease. (Am. J. Hyg., Jan. '49 - J. W. Oliphant et al.)

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Minimal Pulmonary Tuberculosis: With the ever increasing utilization of mass and routine chest roentgenography in industries, schools, hospitals, and communities, many more cases of minimal pulmonary tuberculosis have been detected in recent years. Although in certain cases the roentgenographic appearance of the lesion permits the diagnosis of active disease, in a considerable proportion, however, such a diagnosis can only be made after prolonged observation. The decision concerning which patients should be sent to a sanatorium for observation at the time of the initial diagnosis has always been a difficult one. In the past, many patients with minimal pulmonary tuberculosis have been sent to sanatoriums and discharged as inactive from four to six months later. Others, in contrast, were not hospitalized until the lesion showed evidence of progression. The purpose of this study carried out on 164 patients with minimal tuberculosis admitted to the Rutland State Sanatorium between 1938 and 1945, inclusive, was to explore the relation between the potentialities of a minimal lesion and the age of the patient. Patients leaving the sanatorium against advice are excluded. Except for a few cases in which prolonged postsanatorium observation was deemed unnecessary, all the discharged patients have been followed for a minimal period of two years. The 164 patients are divided arbitrarily, according to their ages, into three groups: those below twenty-five years of age, those from twenty-five to thirty-eight inclusive, and those above thirty-eight.

A lesion was called active when there were demonstrable changes in serial roentgenograms, or when the sputum was positive for bacilli, or both. It was considered progressive when there was roentgenographic evidence of progression during the period of sanatorium residence. The sputum was termed negative only after failure to demonstrate bacilli on at least ten cultures of sputum and three guinea pig inoculations of gastric washings.

An attempt was made to place all the minimal lesions in three pathological categories: the recent infiltrates; the old fibroid "minimal;" and the mixed, which includes all lesions that could not be placed in the former two categories. There were twenty recent infiltrates in the series, of which 12 were found in patients below twenty-five, 8 in patients between twenty-six and thirty-eight, and none in patients above thirty-eight. There were 103 cases with lesions classified as mixed. These constituted 62.7 percent of all lesions in the series, 74.7 percent of all lesions found in patients below twenty-five, 65 percent of those between twenty-six and thirty-eight, and 41.4 percent of those above thirty-eight. Of 41 cases of fibroid "minimal," 24 were in patients above thirty-eight, making up 58.6 percent of all lesions found in that group of patients. Only four cases of fibroid "minimal" were found in those below twenty-five.

It appears safe to conclude that the early infiltrates are chiefly found in young patients, that fibroid "minimal," though not uncommon in young patients, constitutes a large portion of lesions found in the older patients, and that the majority of the latter patients have had tuberculosis long before the time of detection.

The importance of determining the potentialities of a minimal lesion is obvious. Serial roentgenograms and intensive bacteriological study are, perhaps, the only reliable criteria and both of these require a relatively long period to be of any conclusive value. During that period the question of management necessarily arises. Although the sanatorium is undoubtedly the most ideal place for such observation, the socio-economic loss to the patient when kept in a sanatorium cannot be neglected. To send all the patients with minimal lesions to sanatoriums would mean unnecessary hospitalization. Conversely, to advise sanatorium treatment only when there is evidence of progress of the disease would mean losing good opportunities for arresting the disease.

Patients with definite recent infiltrates, with sputum positive for bacilli on the first few initial examinations, and with definite significant symptoms, constitute only a small percentage of all minimal pulmonary tuberculosis. The status of the others remains questionable.

Of the 164 patients, 45 proved to be inactive. Twenty-five of the remaining 119 with active cases had serial roentgenograms compatible with arrested tuberculosis, but were designated as active because of one or two cultures or guinea pig inoculations positive for bacilli. The significance of such findings is still disputable as far as sanatorium treatment is concerned, except in the younger

patients. It may be stated again that 80 percent of those 25 cases were in the group of patients older than thirty-eight. Thus, 42.7 percent of the patients in the series were kept in the sanatorium for an average period of from four to six months just to be told that their lesions were inactive. Had their lesions not been discovered on routine examination, they would have carried on their work and activities normally. Six months of unnecessary sanatorium residence means not only loss to the patient, but also the unnecessary occupation of sanatorium beds. In this study, the age of the patient appeared to be of great significance in the outcome of a minimal lesion. In those below twenty-five, 88.9 percent were active and 48.2 percent of the active cases were progressive; in those above thirty-eight, only 48.8 percent were active and 5 percent of the active cases were progressive. Perhaps it is justifiable to insist on immediate hospitalization of the younger patients. For the older ones, however, especially if their socio-economic conditions are favorable and if they are willing to restrict their activities, it is better to observe them regularly at an outpatient clinic until there is definite evidence of progression.

Determining the nature and character of minimal lesions by roentgenogram remains a difficult problem which cannot be solved quickly. A period of observation is always necessary. This period should be spent preferably in the sanatorium by the younger patient. It seems safe, however, to follow the older ones in the community, thus saving them considerable inconvenience and financial loss. (Am. Rev. Tuberc., Dec. '48 - R. Chang)

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Phrenic Nerve Interruption in the Treatment of Pulmonary Tuberculosis: Because phrenic nerve interruption has been frequently used at Trudeau Sanatorium for over twenty years, a thorough analysis of this material should help in answering the following questions:

1. Is phrenic nerve interruption a useful form of treatment for pulmonary tuberculosis?
2. If so, in what type of case is a satisfactory result most likely to be obtained?
3. What are the early dangers and late sequelae of "temporary" phrenic nerve interruption?

An attempt to answer the first two questions is made here. The third will be considered in subsequent publications.

Of 398 patients subjected to phrenic nerve interruption for pulmonary tuberculosis from 1925 through November 1947, the cases of 292 patients provided adequate data for a detailed statistical study of the procedure. Approximately one half of these fully evaluated patients had an initial good result, while one third remained well without relapse for three postoperative years. Results were slightly better for the temporary operations than for the permanent type. Of the 94 patients with final good results, only 27 had been given six months or more of bed-

rest just prior to phrenic nerve interruption. Cumulative relapse rates following initial good results with phrenic nerve interruption were 18 percent in one and one half years, 25 percent in two years, 34 percent in three years, 37 percent in four years, and 40 percent in five years.

It is concluded that phrenic nerve interruption is beneficial in certain cases of pulmonary tuberculosis and in well selected cases appears to provide a definitive form of treatment. Because of the inadequacy of preoperative bedrest and the absence of dependable controls, however, only limited evidence was found in the present study to support the belief that phrenic nerve interruption provides a widely effective form of treatment for the disease.

The most dependable guide to the selection of patients for phrenic nerve interruption in this series was the finding on serial roentgenograms, over a period of from three to six months, of progressive pulmonary contraction, as distinguished from simple clearing of disease or reduction in cavity size. After hemidiaphragmatic paralysis has been effected, a good final result is more likely (a) when significant hemidiaphragmatic "rise" occurs, preferably above the resting expiratory level; (b) when phrenic nerve interruption is repeated as often as necessary to maintain paralysis for from twelve to eighteen months. (Am. Rev. Tuberc., Dec. '48 - R. S. Mitchell)

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Nonsensitization to Repeated Tuberculin-Testing: Although it has been shown that tuberculin-testing may cause local or systemic flare-ups in patients with proved tuberculosis, the question often arises concerning whether the various tuberculin tests can induce hypersensitivity to tuberculin in nontuberculous individuals.

In this study, 23 nontuberculous infants were tested for hypersensitivity to repeated tests of tuberculin using the patch test on one group and the Mantoux (intradermal) test on another. The same testing procedures were followed in this series, except that several patients of both groups were isolated in a hospital for contagious diseases during periods of contagion, at which time tests were not done.

The Mantoux (intradermal) test using O.T. (prepared by the Bureau of Laboratories of New York City Department of Health) was used on a group of ten infants whose ages ranged from 2 to 9 months, and on one child 3 years of age. In each case a 1:10,000 dilution was first given, and when found to be negative was followed by a 1:1,000, and then a 1:100 dilution. When the child's test proved negative to the latter, it was repeated at 48-hour intervals. The length of time between the first and last test varied from one to six months and the number of tests done from 11 to 60.

In one child there were three occasions on which an area of erythema was noted which disappeared after 48 hours and then was subsequently followed by negative results. In a second child this occurred once and was similarly followed

by negative results giving the impression that it was a mild, local, inflammatory reaction.

The tuberculin patch test (Vollmer) was used on another group of 11 infants ranging in age from 2 to 10 months and on one child of 3 years. It was applied over the interscapular area, read 48 hours after removal, and when negative was immediately followed by another one applied to another area. From eight to 29 patch tests were done on the infants over a period ranging from one to 6 months.

In one child there was one questionable reaction (area of erythema which disappeared within 48 hours on 29 March, but all subsequent tests were negative. In another, questionable reactions occurred on 25 and 29 March and on 11 April, but all others that followed were negative. In a third child, similar questionable reactions occurred on 27 January, 2 February, 5 March, and 15 April, but all other tests were negative. Because of these questionable reactions, this patient (the same as the second child of the first group, mentioned previously) was also tested with O.T. 49 times and except for 1 May when a slight, transient erythema was noted, all tests were negative.

In this series, no evidence of any definite or lasting sensitivity could be detected. It is felt, therefore, that it should be safe to follow any suspicious cases with routine skin testing as long as no evidence of tuberculosis is proved. (J. Pediat., Dec. '48 - J. Schwartzman et al.)

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Availability and Use of Naval Dental Training Films: The educational program of the dental service of the Navy originated with the establishment of a naval dental school in 1923. This school was established for the purpose of providing instruction for dental officers and enlisted dental technicians, and for developing a training program for the personnel who may have duty with the dental service of the Navy.

Visual aids, such as lantern slides and models for demonstrating technics and conditions, were used from the very beginning of the school. Motion pictures were also used as they became available. A motion picture for showing the technic for supplying full and partial dentures immediately after the removal of teeth, was made at the Naval Dental School in 1931. Since then, numerous still and sound motion pictures have been made at the Naval Dental School.

Five new, sound training films in technicolor were completed during the latter part of 1948 at the U. S. Naval Dental School, National Naval Medical Center, Bethesda, Maryland. Copies are to be distributed to the Film Library of the Training Aids Section of each Naval District and River Naval Command. These training films are:

MN-2050B Elastic Impression Materials in Crown, Bridge and Inlay Prosthesis, 30 minutes, color, sound, 1948. A detailed technic for using alginate impression material in crown and bridge procedures.

MN-5368 Root Canal Therapy (Endodontia), 28 minutes, color, sound, 1948. A complete technic for root canal therapy by showing the treatment performed for a patient. Important details are clearly shown with models and animated diagrams.

MN-5369 Operative Dentistry, 40 minutes, color, sound, 1948. The complete operative procedures performed for a patient who receives an amalgam restoration. It includes the application of a rubber dam, preparation of a cavity, application of a matrix, technic for placing an amalgam restoration and the polishing procedures.

MN-5370 Periodontia, 18 minutes, color, sound, 1948. A surgical method for treating periodontal disease. It includes the preoperative, operative, and postoperative treatment of a patient.

MN-5371 Acrylic Crown Construction, 30 minutes, color, sound, 1948. The complete operative and laboratory procedures involved in preparing a tooth and constructing an acrylic jacket crown for a patient.

In addition to the five new films completed by the U. S. Naval Dental School, sufficient copies of "MG-6670 Silicate Cement" and "MG-6763 Dental Amalgam, Failure Caused by Moisture Contamination" are being procured from the National Bureau of Standards for distribution to Naval District and River Naval Command film libraries.

The following is a list of the dental films which are most frequently used for dental training purposes:

Catalog No.	Title and Description
MN-318	Oral Hygiene, 12 minutes, color, silent, narrated, 1942.
MN-1053	Treatment of Jaw Fractures, 25 minutes, color, silent, 1943.
MN-1901	Skeletal Fixation for Fractures of the Mandible, 9 minutes, sound, color, 1943.
MN-2050	Indirect Technique for Precision Construction of Crowns, Bridges and Inlays (using agar base hydrocolloid), 26 minutes, color, silent, 1944.
MN-2050B	Elastic Impression Materials in Crown, Bridge, and Inlay Prosthesis (using alginate impression material), 30 minutes, color, sound, 1948.
MN-2148	Construction of a Partial Maxillary and Mandibular Denture, 24 minutes, color, silent, 1944.
MN-2149	A Technic for Amalgam Restoration, 28 minutes, silent, color, 1944.
MN-2450	Construction of a Maxillary Anterior Fixed Bridge, 49 minutes, silent, color, 1943.
MN-2479	Factors in Construction of Full Maxillary and Mandibular Dentures, 40 minutes, sound, color, 1943.
MN-2607	Duties of a Dental Technician, 18 minutes, black and white, sound, 1944.
MN-2615	The Process of Human Caries, 7 minutes, color, sound, 1943.
MN-3542	Oral Prophylaxis by Dental Technologists, 19 minutes, color, sound, 1945.
MN-4352A	Anterior Acrylic Bridgework, Operative Procedures, 15 minutes, sound, color, 1945.
MN-4352B	Anterior Acrylic Bridgework, Laboratory Procedures, 15 minutes, sound, color, 1945.
MN-4352C	Anterior Acrylic Bridgework, Variation, 10 minutes, sound, color, 1945.
MN-4391B	Prosthesis-Ocular Replacement, 25 minutes, color, sound, 1945.
MN-5368	Root Canal Therapy (Endodontia), 28 minutes, color, sound, 1948.
MN-5369	Operative Dentistry, 40 minutes, color, sound, 1948.
MN-5370	Periodontia, 18 minutes, color, sound, 1948.
MN-5371	Acrylic Jacket Crown Construction, 30 minutes, color, sound, 1948.
MN-6602	Oral Hygiene, Swab Your Choppers, 7 minutes, color, sound, 1948.
MG-6670	Silicate Cement, 18 minutes, color, sound, 1947.
MG-6763	Dental Amalgam, Failure Caused by Moisture Contamination, 15 minutes, color, sound, 1948.

Number of Films of Each Title in Naval District and River Naval Command Film Libraries
(List compiled 31 December 1948)

CATALOG NUMBER	1ND	3ND	4ND	# PRNC	# SRNC	5ND	6ND	8ND	9ND	10ND	11ND	12ND	13ND	14ND	15ND
MN-318	8	1	1	3	2	6	9	0	10	0	1	24	3	4	0
MN-1053	5	9	1	1	1	9	1	0	5	0	4	12	3	7	0
MN-1901	6	12	1	3	1	1	2	0	2	0	6	13	2	8	1
MN-2050	6	10	0	1	1	2	1	0	4	0	8	11	0	7	1
* MN-2050B	2	2	2	5	1	2	2	2	2	1	2	2	2	2	1
MN-2148	7	10	1	3	2	3	1	0	2	0	1	6	3	4	1
MN-2149	6	10	1	3	1	3	1	2	2	0	1	12	3	2	1
MN-2450	4	8	1	3	1	2	1	0	2	0	1	12	3	6	1
MN-2479	6	6	0	3	1	2	1	2	4	0	1	5	2	3	0
MN-2607	7	11	0	4	1	4	0	2	3	0	1	9	2	6	1
MN-2615	7	9	1	4	0	3	1	2	2	0	2	14	2	2	0
MN-3542	4	5	1	3	1	2	2	2	2	0	8	2	4	1	1
MN-4352A	7	10	1	2	1	1	2	4	1	0	5	8	2	1	1
MN-4352B	6	11	1	2	0	1	2	1	1	0	4	10	2	2	0
MN-4352C	5	11	0	2	0	1	2	2	1	0	0	6	1	4	0
MN-4391B	6	10	1	2	0	1	2	0	2	0	1	10	1	1	0
MN-5368	2	3	2	7	1	2	1	2	5	1	3	3	2	2	1
MN-5369	2	3	2	7	1	2	1	2	5	1	3	3	2	2	1
MN-5370	2	3	2	7	1	2	1	2	5	1	3	3	2	2	1
*MN-5371	2	2	2	5	1	2	2	2	2	1	2	2	2	2	1
MN-6602	7	10	7	6	1	8	6	7	7	2	8	8	7	7	2
* MG-6670	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
*MG-6763	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1

Films for the Potomac River Naval Command and the Severn River Naval Command are supplied by the Bureau of Medicine and Surgery.

* In process of being distributed to film libraries.

All dental officers in command or in charge of dental activities of the Navy and Marine Corps are encouraged to use dental training films in the training programs for dental officers and dental technicians.

These films are available as loans for specific dates to the following:

a. Organizations of dental Reserve officers.
b. Groups of dental Reserve officers.
c. Dental colleges.
d. Dental societies.
e. Civilian dental study clubs.
f. Dental fraternities.

Training films will be issued to the following for showing:

a. Dental officers of the regular Navy and the Naval Reserve on active duty.
b. Dental officers of the Naval Reserve in an inactive duty status.
c. Officers or instructors on the staffs of dental colleges.
d. Officers of dental societies or committee members in charge of clinic programs.
e. Representative members of civilian dental study clubs.
f. Officers of dental fraternities.
g. Retired dental officers of the regular Navy and the Naval Reserve.

Training films may be obtained on a temporary loan basis from the headquarters of the nearest Naval District or River Naval Command. Requests should be addressed to the Commandant of the Naval District or River Naval Command. Since all dental films available for temporary loan are in the film libraries of the Training Aids Sections of Naval Districts and River Naval Commands, aviation activities, and Marine Corps activities may obtain them from the same source.

Whenever a temporary loan of a film is not adequate to meet the needs of a Navy or Marine Corps dental activity, copies of films may be requested for permanent loan. Such requests should be addressed in the same manner as for a temporary loan.

The Film Libraries of the Training Aids Sections in the Naval Districts and River Naval Commands will provide prints of films from existing supplies or procure them on quarterly requests through established channels.

The following is a list of addresses to which requests may be directed when films are desired:

Commandant, First Naval District, (Director of Training, Attention: Training Aids Section), North Station Office Building, 495 Summer St., Boston 10, Mass.

Commandant, Third Naval District, (Director of Training, Attention: Training Aids Library), Bldg. 292 New York Naval Shipyard, Brooklyn 1, N. Y.

Commandant, Fourth Naval District, (Director of Training, Attention: Training Aids Section), Bldg. #4, Naval Base, Philadelphia 12, Pa.

Commandant, Fifth Naval District, (Director of Training, Attention: Training Aids Section), Bldg. N-23, Naval Station, Norfolk 11, Va.

Commandant, Sixth Naval District, (Director of Training, Attention: Training Aids Section), U. S. Naval Base, Charleston Naval Base, S. C.

Commandant, Eighth Naval District, (Director of Training, Attention: Training Aids Section), New Federal Bldg., New Orleans 12, La.

Commandant, Ninth Naval District, (Director of Training, Attention: Training Aids Section), Bldg. 1A, Great Lakes, Illinois

Commandant, Tenth Naval District, Attention: District Dental Officer, Navy Number 116, c/o Fleet Post Office, New York, N. Y.

Commandant, Eleventh Naval District, (Director of Training, Attention: Training Aids Section), Naval Base, San Diego 30, Calif.

Commandant, Twelfth Naval District, (Director of Training, Attention: Training Aids Library), Bldg. 7, Treasure Island, San Francisco, Calif.

Commandant, Thirteenth Naval District, (Director of Training, Attention: Training Aids Section), Bldg. 244, Naval Station, Seattle 99, Wash.

Commandant, Fourteenth Naval District, (Director of Training, Attention: Training Aids Library), Navy No. 128, c/o Fleet Post Office, San Francisco, Calif.

Chief of the Bureau of Medicine and Surgery, Attention: Chief of the Dental Division, Navy Department, Washington, D. C. (All requests for loans of films originating within the Potomac River Naval Command, or the Severn River Naval Command should be directed to this address.)

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Naval Dental School Approved by ADA: The Secretary of the Council on Hospital Dental Service of the American Dental Association has announced that the U. S. Naval Dental School, National Naval Medical Center, Bethesda, Maryland, has been inspected and found to merit ADA approval both as a hospital dental service and as a dental intern training activity. The Naval Dental School is part of the National Naval Medical Center at Bethesda, Maryland.

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Naval Reserve Division Established in BuMed: By an order of the Surgeon General on 28 January 1949, a Naval Reserve Division was established as part of the organization of the Bureau of Medicine and Surgery. The Division is to consist of an Office of the Director (Code 36), a Reserve Personnel Branch (Code 361), and a Reserve Training Branch (Code 362).

Captain L. A. Wylie (MC) USNR was appointed Director, Naval Reserve Division, and is to be responsible for the performance of all functions of the Division. Captain Wylie will be located in Building 10, Room 1, and may be reached on telephone Extension 4653.

All organizational elements, functions, records and files pertaining to Naval Reserve personnel (Inactive), except dental, and the enlisted and civilian personnel and office equipment presently assigned to Naval Reserve functions, except dental, are to be transferred to the Naval Reserve Division.

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BuMed-41-MFD/NH77/A1-1 26 January 1949

To: The Secretary of the Navy
Via: The Chief of Naval Operations

Subj: Disestablishment of U.S. Naval Hospital, Houston, Texas; Recommendation for

Refs: (a) Memorandum from the President to the Secretary of the Navy dated 20 December 1948
(b) Op13-1D-psp, Serial 353913, 7-4-56, dated 14 July 1945

1. The President, by reference (a), directed that the U.S. Naval Hospital, Houston, Texas, which was established by reference (b), be transferred to the Veterans Administration as soon as possible.

2. Arrangements have been made with the Veterans Administration to effect an orderly replacement of the present staff of the hospital with Veterans Administration personnel in order that the treatment of beneficiaries of the Veterans Administration may be continued without interruption. It has been mutually agreed that this replacement shall be completed by 15 April 1949.

3. It is recommended, therefore, that the U.S. Naval Hospital, Houston, Texas, be disestablished on 15 April 1949 and transferred to the Veterans Administration on that date. --BuMed. C.A. Swanson

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BUMED CIRCULAR LETTER 49-8 4 February 1949

To: All Medical Department Activities

Subj: Shipment of Personal Effects of Deceased Active Duty Naval Personnel

Refs: (a) Change No. 84, Navy Shipping Guide, Part I, Article 1820 (6) (b)
(b) BuMed Cirltr No. 48-121 dated 8 November 1948
(c) Advance notice of change to Navy Shipping Guide, Change No. 82
(d) Paragraph 3428.1, Manual Medical Department

1. Reference (b) is hereby cancelled. Reference (a) which supersedes reference (c) is quoted below for the information and guidance of all concerned.

"(b) Effects of deceased personnel. - - Transportation of effects of deceased officers and enlisted personnel of the Navy and of officers and enlisted personnel of the Naval Reserve who die while on duty is authorized. When the remains are shipped by express and when

personal effects accompany the remains the Railway Express Agency allows up to 150 pounds as free transportation. Therefore, in packing effects which are to move by express with the remains, the weight will be kept within 150 pounds. Any effects in excess of 150 pounds will be separately packed and shipped under government bill of lading. When there is no doubt as to the next of kin of the deceased, personal effects within continental United States will be shipped as soon as possible without awaiting specific authorization from the Navy Department. Personal effects returned from points outside continental United States in the Atlantic Ocean area will be forwarded to the Supply Officer, Naval Supply Center, Norfolk, Va., and in the Pacific Ocean area to the Personal Effects Distribution Center, Naval Supply Depot, Clearfield, Ogden, Utah."

2. Appropriate changes will be made in the Manual of the Medical Department and released to the Naval service in the near future. --BuMed. H.L. Pugh

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BUMED CIRCULAR LETTER 49-9 Joint Letter 7 February 1949

To: MOinCs, NavHosps; and COs, All MarCorps Activities; Continental U.S.

Subj: Disposition of Enlisted Men of the Marine Corps Disabled in Line of Duty

Refs: (a) Joint MarCorps-BuMed Letter of 16 Mar 1944; 1535-200 DB-311-ee, Letter of Instruction No. 683; BuMed Circ. Ltr. No. 44-46
(b) Joint Letter, BuPers-BuMed-MarCorps, dtd 22 Nov 1948; BuPers Pers-66-JMS, P3-5, BuMed-3352-FGS-keh P3-5 (BuMed Circ. Ltr. No. 48-128), MarCorps-DKG-356-mla 1500-120

1. Reference (a) is hereby cancelled in view of the provisions of reference (b).

--MarCorps. C.B. Cates --BuMed. J.T. Boone

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BUMED CIRCULAR LETTER 49-10 8 February 1949

To: All Medical Department Officers

Subj: Medical Research in Ships and Shore Stations Other Than Hospitals

Ref: (a) BuMed C/L 48-46 of 26 April 1948
(b) BuMed C/L 48-133 of 29 Nov 1948

1. Reference (a) stresses the importance of research by the Medical Department of the Navy. Reference (b) implements clinical research in naval hospitals.

2. Medical Department officers on board ship or attached to shore stations are similarly encouraged to undertake appropriate investigations, especially those relating to the immediate naval environment.

3. Research proposals should be forwarded via the Commanding Officer to the Bureau for consideration. If approved, such proposals will be formally established as projects and the Bureau of Medicine and Surgery will furnish such assistance and consultation as may be indicated. --BuMed. J. T. Boone

Note: Each proposal should contain information concerning the following: (1) Project title. (2) Location(s) of study. (3) Estimated duration. (4) Objective(s) and experimental design. (5) Requirements to be provided: (a) subjects, (b) material, and (c) funds (requiring allocation). (6) Principal investigator. (7) Collaborator(s). (8) Consultant(s).

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BUMED CIRCULAR LETTER 49-11 8 February 1949

To: BuMed Management Control Activities

Subj: Manual of the Medical Department, USN; Reprinting of

It is stated in this letter that a complete reprint of the Manual of the Medical Department in double column, 8 ins. x 10-1/2 ins. page size is contemplated. Reprinting of the Manual will permit a change in format if a change is desired. Comments and recommendations are requested concerning whether a new numbering system should be adopted or the present system be retained. Suggestions regarding the index are also desired. Comments and recommendations should reach BuMed, Code 2113, by 25 February 1949.

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BUMED CIRCULAR LETTER 49-12 9 February 1949

To: Medical Officers in Command, All Naval Hospitals

Subj: Transcript of Intern Service (NavMed-1293)

Encl: 1. (HW) Initial supply of NavMed-1293 (Hospitals approved for Intern Training).

1. Upon the satisfactory completion of the prescribed course of Intern training, the Bureau will provide each Naval Intern with a Certificate of Internship signed by the Surgeon General of the Navy. This document will be forwarded to the Intern via official channels and shall be countersigned by the Medical Officer in Command prior to delivery. In the event the certificate is withheld from delivery by the Medical Officer in Command for any reason, it shall be expeditiously returned to the Bureau with appropriate comment.

2. In the event Interns subsequently file application with State Boards for medical licensure, it is necessary that credentials include information supplementary to the Certificate of Internship. Therefore, at the time of delivery of the Certificate of Internship, medical officers in command shall in addition provide each Intern with a "Transcript of Intern Service" setting forth in detail a record of Services attended and the period devoted to each Service. This transcript shall be signed by the Chiefs of the various Services, countersigned by the Medical Officer in Command and bear the official seal of the hospital.

3. In the interests of completeness and uniformity, a standard form (NavMed-1293 Transcript of Intern Service) has been designed for use by all addressees. An initial supply of the form is enclosed herewith. Requisitions for additional copies should be addressed to the Bureau.

4. A copy of each such transcript issued shall be forwarded for the files of the Bureau of Medicine and Surgery (Attn: Code-3424).

--BuMed. C.A. Swanson

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BUMED CIRCULAR LETTER 49-13 9 February 1949

To: All Holders of the Manual of the Medical Department

Subj: Advance Change 3-9, MMD.

Encl: 1. (HW) Subject Change

1. The enclosed Advance Change 3-9 is effective immediately. It shall be recorded on the "Record of Changes" page in the Manual. The individual paragraph changes are to be inserted in their proper places in the Manual text. At a later date, these changes will be incorporated in printed page change 3.

--BuMed. H. L. Pugh

Note: This letter together with the enclosure, consisting of 2 pages, will be distributed by BuMed as soon as it is received from the printer.

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BUMED CIRCULAR LETTER 49-14 14 February 1949

To: MOinCs, NavHosps within Continental U. S.; Commanders, All Naval Training Centers; COs, All MarCorps Activities, Continental U.S.

Subj: Statistical Reporting of Patients Invalided from the Service

Ref: (a) BuMed C/L 48-128 (Joint BuPers, MarCorps, BuMed ltr) of 22 Nov 1948.

In this letter it is stated that (1) by reference (a) addressees were authorized to take final action in certain types of Reports of Medical Survey, and (2) in other types final action was reserved by the Navy Department, but medical officers in command were authorized to transfer selected patients in duty status to a receiving station or Marine barracks to await action on the Report of Medical Survey. Instructions are given which apply to reporting these types of patients on NavMed-Fa, Individual Statistical Report of Patient, and NavMed-I, Report of Patients.

BUMED CIRCULAR LETTER 49-15 15 February 1949

To: Medical Officers in Command, U. S. Naval Hospitals

Subj: Naval Hospital Organization Charts and Personnel Listing Sheets, Procedure for the Regular Preparation and Submission of

Ref: (a) N.C.P.I. 156. 11-5-a(1).

Encl: 1. (HW) Sample Functional Organization Sub-Chart.

This letter states that in order to obtain data in essentially the same form from all hospitals, the reporting procedure outlined therein, which follows very closely and will meet the requirements of reference (a), is being established. It is stated also that BuMed will not require submission of new charts and listings in connection with a classification survey conducted by an Area Wage and Classification Office, provided the activity certifies that the charts and listings (with respect to the number and types of positions) on file in the Bureau are still current. It is also emphasized that a complete, accurate charting and personnel listing are desired.

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